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Sex differences in the risk of coronary heart disease associated with type 2 diabetes: a Mendelian Randomization analysis

Sex differences in diabetes and heart disease

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Abstract

Objective: Observational studies have demonstrated that type 2 diabetes is a stronger risk factor for coronary heart disease (CHD) in women compared with men. However, it is not clear whether this reflects a sex differential in the causal effect of diabetes on CHD risk or results from sex-specific residual confounding.

Methods: Using 270 single nucleotide polymorphisms (SNPs) for type 2 diabetes identified in a type 2 diabetes genome-wide association study, we performed a sex-stratified Mendelian randomization (MR) study of type 2 diabetes and CHD using individual participant data in UK Biobank (N=251,420 women and 212,049 men). Weighted-median, MR Egger, MR-PRESSO and radial MR from summary-level analyses were used for pleiotropy assessment.

Results: MR analyses showed that genetic risk of type 2 diabetes increased the odds of CHD for women (odds ratio [OR] 1.13, 95% confidence interval [CI] 1.08-1.18 per 1-log unit increase in odds of type 2 diabetes) and men (OR 1.21, 95% CI 1.17-1.26 per 1-log unit increase in odds of type 2 diabetes). Sensitivity analyses showed some evidence of directional pleiotropy, however, results were similar after correction for outlier SNPs.

Conclusions: This MR analysis supports a causal effect of genetic liability to type 2 diabetes on risk of CHD that is not stronger for women than men. Assuming a lack of bias, these findings suggest that the prevention and management of type 2 diabetes for CHD risk reduction is of equal priority in both sexes.

Introduction

Type 2 diabetes is a major risk factor for coronary heart disease (CHD)(1). Meta-analysis of observational studies demonstrates that type 2 diabetes is associated with a 44% greater relative risk of CHD in women compared with men(2). However, whether this reflects sex differences in the causal effect of type 2 diabetes on CHD or arises from confounding in observational studies is not well understood. Most observational studies adjust for traditional cardiovascular risk factors, yet novel biomarkers, social and behavioral factors, or women-specific risk factors, such as gestational diabetes, are not generally adjusted for and may explain some of the sex difference(3–5). Sex differences in screening for and treatment of type 2 diabetes might also contribute to the greater excess risk of CHD conferred by type 2 diabetes among women relative to men(6).

Mendelian randomization (MR) analysis exploits the natural random allocation of genetic variants at conception and is an increasingly utilized approach that can limit potential confounding in human research(7). Under the assumption that differences in the risk of disease arising from genotype mimic changes in the risk of disease acquired during life, MR can be used to detect causal effects. Recent MR studies support a causal relationship between genetic predisposition to type 2 diabetes and CHD(8,9). However, these studies did not evaluate sex differences in the causal role of type 2 diabetes in CHD risk. If type 2 diabetes has a stronger causal effect on CHD risk in women compared with men, randomly allocated genetic variants that are risk alleles for type 2 diabetes should also be more strongly associated with the risk of CHD in women than in men. Therefore, in this study we conducted a MR analysis to examine the sex-specific causal effect of the genetic risk of type 2 diabetes on CHD.

Methods

Data sources and study participants

Data from the UK Biobank and a consortium of genome-wide association studies (GWAS) for type 2 diabetes were used. The UK Biobank is a large prospective study of over 500,000 individuals(10). Baseline data collection in the UK Biobank was conducted between 2006 and 2010 across 22 assessment centers. Participants aged 37 to 73 completed touchscreen questionnaires, were interviewed by trained research nurses, had physical measurements taken and blood samples extracted and frozen. The presence of type 2 diabetes and CHD was self-reported at study baseline and confirmed by a trained nurse. Genotyping was performed using the Affymetrix UK BiLEVE Axiom array or the Affymetrix UK Biobank Axiom® array. A combined reference panel including UK10K samples was used for imputation(11). In accordance with the National Research Ethics Service and the governing Research Ethics Committee of UK Biobank, generic Research Tissue Bank approval was obtained, and study participants provided written informed consent(10).

For the present study, we included individual-participant data on 463,469 UK Biobank participants who had concordant genetic and self-reported sex, who clustered with the Great Britain population in 1000 Genomes(12), whose genetic data was of sufficient quality(13), and who provided data on type 2 diabetes and CHD at baseline. Individuals with self-reported type 1 diabetes, gestational diabetes only, or a diabetes diagnosis prior to the age of 18 were excluded. CHD was defined as self-reported history of angina or myocardial infarction, and linkage with hospital admissions data and the national death register was used to also identify incident diagnoses of CHD after the baseline visit using international classification of disease (ICD) 9 or 10 codes (ICD9 410-414, ICD10 I20-I25) using follow-up data from recruitment through the end of February 2016 (mean 5.3 [SD 2.4] years), with N=3453 incident cases of CHD for women and

N=7420 incident cases for men. Myocardial infarction was also defined using the UK Biobank algorithm (https://biobank.ctsu.ox.ac.uk/crystal/crystal/docs/alg_outcome_mi.pdf).

Sex-specific summary-level data (ß-coefficients and standard errors) for the genetic contribution of type 2 diabetes risk were obtained from the European DIAMANTE (DIAbetes Meta-Analysis of Trans-Ethnic association studies) GWAS of type 2 diabetes cases (N=30,053 women and 41,846 men) and controls (N=434,336 women and 383,767 men) of European descent(14). The UK Biobank was excluded from GWAS estimates used in our analyses to avoid sample overlap.

Mendelian randomization and selection of SNPs for analyses

Mendelian randomization studies exploit the random assortment and independent inheritance of genetic variants in the population, which removes bias due to reverse causation and, if conducted appropriately, greatly reduces bias from residual or unmeasured confounding(15). However, three key assumptions must be met for genetic variants to serve as instrumental variables of an exposure in MR analyses (Supplemental Figure 1)(16). First, the variants must be associated with the exposure of interest; second, they must not be associated with confounders of the relationship between the exposure and the outcome; third, they must be independent of the outcome except for their association via the exposure. This third assumption relates to the issue of horizontal pleiotropy, in which one or more variants used in the instrumental variable influences the outcome via a pathway other than the exposure of interest. When horizontal pleiotropy has a net effect to bias the properties of the genetic instrument, the summary MR estimate can be biased either towards or away from the null. In this situation, horizontal pleiotropy leads to bias of the underlying ‘true’ causal effect and it is termed unbalanced horizontal, or directional, pleiotropy.

In this study, we used data from the UK Biobank for individual-participant MR analysis. SNPs with significant associations ($p<5x10^{-8}$) with type 2 diabetes from the sex-combined European DIAMANTE GWAS were selected (Supplemental Table 1). We assessed linkage disequilibrium (LD; $r^2>0.2$) using PLINK(17) on a reference panel consisting of a random selection of 50,000 individuals from UK Biobank. Of 291 genome-wide significant SNPs from the European DIAMANTE GWAS, 270 were found in UK Biobank that were bi-allelic, were not in LD, and were not derived from GWAS that adjusted for body mass index. The SNPs were aligned to the same effect allele, and effect allele frequencies were checked for concordance. These 270 SNPs were used to generate sex-specific weighted genetic risk scores as the instrumental variable for analyses(18). Individual SNPs were coded as 0, 1, or 2 depending on the number of type 2 diabetes risk alleles. Each SNP was weighted by the corresponding sex-specific ß-coefficient obtained from the European DIAMANTE GWAS and then summed for all SNPs. This method reduces the risk of false positive results and bias toward the confounded observational association that may occur when all data (SNPs, exposure, outcome) are obtained from a single sample(19).

Statistical analysis

The strength of the genetic risk score as an instrument for type 2 diabetes was assessed using the F-statistic, where an F-statistic greater than 10 provides evidence against the possibility of bias arising due to a weak instrument(20). The association of sex-specific genetic risk scores with potential confounders was evaluated to assess the validity of the second assumption of MR (i.e., the genetic instrument is not associated with potential confounders) and was also compared with the observational association of type 2 diabetes status with potential confounders.

Two-stage residual inclusion estimation using logistic regression at the second stage(21) and Terza standard errors(22) evaluated the association of the genetic risk scores for type 2

diabetes with CHD to estimate the odds of CHD per 1-log unit increase in the odds of type 2 diabetes. This method includes first-stage residuals to correct for endogeneity(21), since application of traditional instrumental variable estimation approaches can be problematic for models including a binary exposure and a binary outcome(23). Models were adjusted for age, genotype array, and the first four principal components of ancestry.

To assess and account for potential directional horizontal pleiotropy, we also performed summary-level MR analyses using SNP to type 2 diabetes estimates from DIAMANTE and SNP to CHD estimates in UK Biobank. For summary-level analyses, we obtained odds ratios (ORs) and 95% confidence intervals (CI) for the causal effect of a 1-log unit increase in the odds of genetic liability to type 2 diabetes on the odds of CHD using the weighted-median, MR Egger, Mendelian randomization pleiotropy residual sum and outlier (MR-PRESSO), and radial MR methods(24–27). The weighted-median method calculates a median of the SNP-specific causal estimates from the ratio method for each SNP(25). It has been shown to yield consistent estimates when the weights of up to half the instruments are not valid. The MR Egger method is equivalent to an inverse-variance weighted method but does not constrain the intercept to zero, and as such, the MR Egger estimate is the slope of the modified linear regression equation and the intercept represents the average pleiotropic effect across SNPs(24). A non-zero intercept provides evidence of unbalanced horizontal pleiotropy, and the slope of the regression coefficient should provide an estimate that is free from bias induced by unbalanced horizontal pleiotropy. Analyses were conducted using the 'MendelianRandomization' package in R Studio version 1.2.1206. The MR-PRESSO test detects and corrects for horizontal pleiotropy and was performed using the 'MRPRESSO' package in R(26). The first part of the test (MR-PRESSO global test) identifies the presence of horizontal pleiotropy, the second part corrects the causal estimate for identified

pleiotropy via outlier removal, and the third part (MR-PRESSO distortion test) tests whether the causal estimate significantly differs before and after correction. Additional analyses for pleiotropy assessment used radial MR Egger models to identify outliers in the UK Biobank analysis using the 'WSpiller/RadialMR' package in R with modified second order weights(27), and analyses were repeated after exclusion of sex-specific outliers. P-values for the test of interaction for estimates from separate analyses was used to assess interaction by sex for each analysis(28).

Results

Characteristics of the UK Biobank participants are presented in Table 1 and Supplemental Table 3. The mean age was 57 (standard deviation [SD] = 8) years and 46% of participants were men. The prevalence of type 2 diabetes was 4% in women and 8% in men. CHD was documented among 5% of women (N=12 716) and 12% of men (N=26 344), with myocardial infarction diagnosed in 1.5% of women (N=3807) and 6% of men (N=12 871). Both women and men with CHD were more likely to have traditional CHD risk factors (older age, type 2 diabetes, history of smoking, dyslipidemia, and hypertension) (Supplemental Table 3).

The sex-specific 270-SNP genetic risk score showed a strong association with type 2 diabetes in both sexes (F-statistic 683 for women and 1005 for men, Supplemental Table 2), thus satisfying the first assumption of MR that the genetic instrument is associated with the exposure. We evaluated whether the apparent difference in instrument strength by sex was due to sex differences in the prevalence of type 2 diabetes. In a random subset of UK Biobank participants with 750 cases of type 2 diabetes for both women (N=18 493) and men (N=9100), the adjusted F statistic of 47 (R-squared 0.02) for women, and adjusted F statistic 45 (R-squared 0.03) for men were similar (data not shown). Thus, because the difference in instrument strength by sex is a

product of greater prevalence of type 2 diabetes in men, it is not likely to appreciably affect the comparative validity of estimates derived from MR analyses.

Potential confounders were similarly distributed across quartiles of the genetic risk score for both women and men (Table 2). Conversely, conventional observational analyses showed that type 2 diabetes status was strongly associated with all potential confounders assessed (Table 2), highlighting the need for instrumental variables in this setting.

Individual-participant results from TSRI analyses in UK Biobank showed similar effects of genetic risk of type 2 diabetes on CHD for each sex (OR 1.13, 95% CI 1.08-1.18 for women; OR 1.21, 95% CI 1.17-1.26 for men, Table 3). Sensitivity analyses using the weighted median method showed attenuated results (OR 1.04, 95% CI 1.00-1.08 for women; OR 1.06, 95% CI 1.03-1.09 for men, Table 3). Using MR Egger, evidence of directional pleiotropy was observed in women (OR 1.01, 95% CI 0.96-1.06 and intercept 0.004, 95% CI 0.000 to 0.008, Table 3) and men (OR 1.00, 95% CI 0.96-1.04 and intercept 0.008, 95% CI 0.004 to 0.011, Table 3). Results from MR-PRESSO after outlier correction were slightly attenuated compared with those from TSRI analyses for both women (three outliers removed, OR 1.08, 95% CI 1.05-1.13) and men (five outliers removed, OR 1.13, 95% CI 1.10-1.17, Table 3). Analyses excluding SNPs from the genetic instrument that were identified as outliers by radial MR showed similar effect estimates as the TSRI results: OR 1.09, 95% CI 1.05-1.14 for women; OR 1.24, 95% CI 1.20-1.29 for men (Table 3). We employed additional measures to assess for heterogeneity based on MR-Egger regression, including the Cochran Q-test and I-squared statistic. The Q-test showed evidence of heterogeneity in the effect of type 2 diabetes SNPs on CHD for both women (Q-statistic 395.8) and men (Q-statistic 666.0). The I-squared (I^2) statistic measures heterogeneity in the genetic associations with the exposure, and results (I^2 84.7% for women and 87.1% men) showed some evidence of

heterogeneity in the associations of SNPs with type 2 diabetes. Such heterogeneity could be reflective of multiple causal pathways between type 2 diabetes and risk of CHD.

Discussion

In this MR study of the sex-specific effect of type 2 diabetes on CHD, we found that genetic predisposition to type 2 diabetes does not confer a greater excess risk of CHD for women than for men. While our results are consistent with previous sex-combined MR studies providing support for a causal role of type 2 diabetes in CHD risk(8,9), the finding that the causal effect of genetic liability to type 2 diabetes on CHD risk is not stronger for women than men is novel and differs from sex-specific estimates from the accumulated observational evidence(2). This includes a recent analysis in the UK Biobank, which showed a stronger association of type 2 diabetes with CHD for women than men(29).

There are several potential explanations for the differences between the findings of our MR study and the observational evidence. As with any observational study, studies of sex differences in the association of type 2 diabetes with CHD may not have controlled for all relevant confounders or may have controlled for confounders that were poorly measured, leading to residual confounding. If this residual confounding differs between the sexes, a sex difference in the observational association of type 2 diabetes with CHD could arise. For example, men are typically at higher absolute risk of CHD, and the prevalence of many cardiovascular risk factors is higher for men than for women(1). However, cardiovascular risk factors including type 2 diabetes appear to confer a greater relative CHD risk for women than for men in observational analyses(29). Furthermore, among individuals with type 2 diabetes compared to those without type 2 diabetes, several studies have shown that the differences in cardiovascular risk factors including blood pressure, dyslipidemia, and particularly anthropometric variables are greater among women than

men(3,6). Although women generally display a more favorable cardiometabolic risk profile than men, this favorable risk profile declines and ultimately reverses as glycemic control deteriorates(30).

Yet observational evidence of sex differences in the association of other major risk factors with CHD is not universally observed, suggesting mechanisms other than confounding alone may be involved. An alternative explanation is that sex differences in the effect of diabetes on CHD risk seen in observational studies reflect the more adverse deterioration in cardiovascular risk profile along the glucose intolerance spectrum in women than men. A recent MR study showed that the association of BMI with the risk of diabetes was stronger for women than men(31). Accordingly, a pathway of type 2 diabetes progression and glycemic dysregulation that leads to more adverse complications of diabetes for women than men may underpin the observational findings, rather than a direct sex difference in the effect of diabetes on CHD risk.

Furthermore, women may be perceived as having lower cardiovascular risk and consequently, type 2 diabetes and comorbid cardiovascular risk factors may be treated less aggressively(32,33). Guidelines for the diagnosis and treatment of type 2 diabetes and CHD are not sex-specific; our results of a similar causal association of type 2 diabetes with CHD by sex would support the notion that for a given state of glycemic dysregulation and burden of cardiovascular risk factors, prevention and management of type 2 diabetes for the reduction of CHD risk should be of equal priority for both women and men. In addition, sex-specific confounders, such as reproductive factors including gestational diabetes, are rarely adjusted for in observational studies that include both sexes; this could inflate the association of type 2 diabetes with CHD in women if the cumulative duration of the exposure to diabetes is greater, on average, among women than men. Sex-specific residual confounding may therefore explain some of the

discrepancy between the MR and observational evidence. Alternatively, the discrepancy might arise if the MR analysis does not account for genetic variation in the risk of type 2 diabetes that derives from sex chromosomes, as the GWAS data includes only autosomal SNPs. For example, a recent MR study observed a causal association of genetically determined testosterone (X chromosome) with increased type 2 diabetes risk for women but not for men(34). Multiple other mechanisms could also play a role in conferring higher CHD risks for women with type 2 diabetes compared with men independent of glucose dysregulation or diabetes, including sex differences in microvasculature such as vascular responsivity to aldosterone(35).

The diagnosis of type 2 diabetes is defined by a cut-point along a continuum of glycemia that is based on the risk of associated complications such as retinopathy(36). Accordingly, an individual with borderline glycemia who is not yet diagnosed with type 2 diabetes may display phenotypic and genetic similarity when compared to an individual with diagnosed diabetes. Exposure misclassification of this type would tend to bias individual-participant MR estimates toward the null, leading to underestimation of the MR results. In our individual-participant MR, this scenario would only affect our conclusion when pre-diabetes affected a differential proportion of women and men in the study population. Of note, this should not influence summary-level MR results as the exposure is fully defined by genotype.

There are several strengths of our study, including the use of MR, which under specific assumptions can be used to test the hypothesis that a particular risk factor is causal for an outcome(16). In accordance with the first assumption of MR, the sex-specific genetic risk scores were very strong instruments for type 2 diabetes for both women and men. Meeting the second and third assumptions of MR, the genetic risk scores were shown to be broadly independent of measured potential confounding factors. Furthermore, for both women and men, results of

sensitivity analyses after correction for outliers were similar to initial results. However, there are also limitations of our study. Although the genetic risk scores were strong instruments for type 2 diabetes, our instruments may have been underpowered to detect modest differences in sex-specific causal effects. Furthermore, our analysis used genetic risk scores derived from 270 genome-wide significant type 2 diabetes SNPs in the sex-combined European DIAMANTE GWAS(14). Genetic instruments obtained from the SNPs that are associated with type 2 diabetes in sex-specific GWAS could also have been constructed. However, the European DIAMANTE GWAS observed only one significant sex-differentiated SNP(14) and thus, the impact of the use of a sex-combined instrument is unlikely to have changed our results substantially. Moreover, such an instrument would not permit direct comparison of sex differences in the overall genetic predisposition to type 2 diabetes, but instead compares the causal effect of two distinct sex-specific instruments on CHD risk.

SNPs included in the genetic instruments for type 2 diabetes may affect CHD risk via pathways separate from their effect on type 2 diabetes risk, and these pathways could differ by sex. For example, there was some evidence of directional pleiotropy using MR Egger. However, the intercept for both men and women neared zero and MR-Egger generally lacks power. Moreover, results from outlier-robust sensitivity analyses were more similar to the overall results. This suggests that our primary results are in fact robust and that MR Egger results may have been influenced by sensitivity of this method to extreme outliers(37).

These results might reflect multiple different scenarios(38), some of which may have downstream effects on type 2 diabetes risk and may differentially affect CHD risk by sex. Taken together, we cannot exclude a sex-specific causal effect via other pathways not captured in our genetic instrument. Of note, our instrumental variables for type 2 diabetes were derived from the

DIAMANTE GWAS effect estimates without adjustment for BMI since the influence of BMI on type 2 diabetes risk may be sex-differential(31). Considering the important role of BMI in type 2 diabetes risk, adjusting for measures of adiposity in the type 2 diabetes GRS could bias a true differential effect of type 2 diabetes on CHD to the null. In addition, the UK Biobank and the European DIAMANTE GWAS used for our analyses include primarily European populations, and therefore, we cannot assess sex differences in the causal effect of type 2 diabetes with CHD across ethnicities. Furthermore, despite the large sample size of the UK Biobank, a low overall response rate of ~5.5% limits the generalizability of our results. Considering that the participating population is unlikely representative of the general UK population, as recently demonstrated(39), it is possible that our findings might be biased if there is a sex-specific selection bias that is associated with both the exposure and the outcome. Finally, a recent study demonstrated an association of autosomal loci with sex, which may introduce bias due to sex differences in study participation(40). If risk alleles for type 2 diabetes were associated with study participation in a sex-specific manner, this may have resulted in an inability to consistently detect a sex difference in the causal effect of type 2 diabetes with CHD in our MR analyses.

Conclusion

The present MR analysis supports a causal effect of type 2 diabetes on the risk of CHD, with similar effects seen between women and men. In the absence of bias, these findings suggest that the prevention and management of type 2 diabetes for the reduction of CHD risk should be of equal priority for both women and men.

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Disclosures

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Author Contributions

T.M.P. analyzed the data, wrote the manuscript, and contributed to study design and conception. M.V.H. contributed to study design and reviewed/edited the manuscript. J.B.R. contributed to study design and reviewed/edited the manuscript. T.P. contributed to study design and data analysis and reviewed the manuscript. V.F. contributed to data analysis and reviewed the manuscript. C.M.L. reviewed/edited the manuscript. F.W.A. reviewed/edited the manuscript. C.P.N. reviewed/edited the manuscript. N.J.S. reviewed/edited the manuscript. M.I.M. contributed data and reviewed/edited the manuscript. A.M. contributed data and reviewed/edited the manuscript. G.D.S. reviewed/edited the manuscript. M.W. contributed to study design and reviewed/edited the manuscript. L.M.O.K. contributed to study design and wrote the manuscript. S.A.E.P. contributed to study design, data analysis, and wrote the manuscript.

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Table 1. Population Characteristics, UK Biobank (N=463 469)

	Women (N=251 420)		**Men (N=212 049)**	
Age, mean (SD*), years	56.6	(7.95)	57.0	(8.12)
Array type, No. (%)				
BiLEVE	24 920	(9.9)	24 897	(11.7)
Axiom	226 489	(90.1)	187 147	(88.3)
Type 2 diabetes, No. (%)	9964	(4.0)	16 917	(8.0)
Body mass index, mean (SD), kg/m^2	27.0	(5.1)	27.9	(4.2)
Waist circumference, mean (SD), cm	84.6	(12.5)	97.1	(11.4)
Smoking history, No. (%)				
Never	146 521	(58.3)	102 139	(48.2)
Previous	81 252	(32.3)	82 970	(39.1)
Current	22 574	(9.0)	26 011	(12.3)
Dyslipidemia, No. (%)	25 549	(10.2)	33 843	(16.0)
Hypertension, No. (%)	57 721	(23.0)	64 668	(30.5)
Systolic BP†, mean (SD), mmHg	135.3	(19.1)	141.1	(17.4)
Diastolic BP, mean (SD), mmHg	80.5	(9.9)	84.0	(9.9)
Coronary heart disease, No. (%)	12 716	(5.1)	26 344	(12.4)
Myocardial infarction, No. (%)	3807	(1.5)	12 871	(6.0)
Angina, No. (%)	4864	(1.9)	10 219	(4.8)

*SD: standard deviation; †BP: blood pressure

Table 2. Association of sex-specific genetic risk scores (270 SNPs*) for type 2 diabetes, by quartile, with potential confounders, and association of observational type 2 diabetes with potential confounders in the UK Biobank.

Genetic type 2 diabetes risk					Type 2 diabetes diagnosis		
Quartiles of genetic risk score					Observational association		
Women	Q1	Q2	Q3	Q4		No Diabetes	Diabetes
Quartile range	13.82-<15.94	15.94-<16.31	16.31-<16.68	16.68-<18.71			
No. participants	62 856	62 854	62 855	62 855	No. participants	241 456	9964
Height, mean (SD†), cm	162.8 (6.2)	162.6 (6.3)	162.5 (6.2)	162.5 (6.3)	Height, mean (SD), cm	162.7 (6.2)	161.4 (6.3)
Weight, mean (SD), kg	70.8 (13.8)	71.3 (13.9)	71.6 (14.0)	72.0 (14.1)	Weight, mean (SD), kg	70.9 (13.5)	84.6 (18.2)
Body mass index, mean (SD), kg/m^2	26.7 (5.1)	27.0 (5.1)	27.1 (5.2)	27.3 (5.2)	Body mass index, mean (SD), kg/m^2	26.8 (5.0)	32.5 (6.6)
Waist, mean (SD), cm	83.7 (12.3)	84.3 (12.4)	84.8 (12.5)	85.5 (12.7)	Waist, mean (SD), cm	84.0 (12.0)	99.1 (14.8)
Current smoking, N (%)	5543 (8.8)	5564 (8.9)	5755 (9.2)	5781 (9.2)	Current smoking, N (%)	21 585 (8.9)	1058 (10.6)
Dyslipidemia, N (%)	5796 (9.2)	6108 (9.7)	6497 (10.3)	7148 (11.4)	Dyslipidemia, N (%)	51 833 (21.5)	5888 (59.1)
Hypertension, N (%)	13 190 (21.0)	14 032 (22.3)	14 769 (23.5)	15 730 (25.0)	Hypertension, N (%)	22 024 (9.1)	3525 (35.4)
Type 2 diabetes, N (%)	1204 (1.9)	1898 (3.0)	2560 (4.1)	4302 (6.8)			
Coronary heart disease, N (%)	3008 (4.8)	3077 (5.0)	3247 (5.2)	3348 (5.3)	Coronary heart disease, N (%)	10 823 (4.5)	1893 (19.0)
Men	Q1	Q2	Q3	Q4		No Diabetes	Diabetes
Quartile range	14.58-<16.67	16.67-<17.05	17.05-<17.43	17.43-19.54			
No. participants	53 014	53 011	53 012	53 012	No. participants	195 132	16 917
Height, mean (SD), cm	176.0 (6.8)	175.8 (6.8)	175.8 (6.8)	175.7 (6.8)	Height, mean (SD), cm	175.9 (6.8)	174.7 (6.8)
Weight, mean (SD), kg	85.9 (14.4)	86.0 (14.3)	86.3 (14.3)	86.5 (14.2)	Weight, mean (SD), kg	85.4 (13.7)	95.4 (17.5)
Body mass index, mean (SD), kg/m^2	27.7 (4.3)	27.8 (4.3)	27.9 (4.3)	28.0 (4.2)	Body mass index, mean (SD), kg/m^2	27.6 (4.0)	31.2 (5.2)
Waist, mean (SD), cm	96.8 (11.5)	96.9 (11.4)	97.2 (11.3)	97.4 (11.2)	Waist, mean (SD), cm	96.2 (10.8)	106.3 (13.2)
Current smoking, N (%)	6417 (12.1)	6492 (12.2)	6670 (12.6)	6555 (12.4)	Current smoking, N (%)	23 931 (12.3)	2203 (13.0)

Dyslipidemia, N (%)	7925 (14.9)	8349 (15.7)	8473 (16.0)	9096 (17.2)	Dyslipidemia, N (%)	27 627 (14.2)	10 749 (63.5)
Hypertension, N (%)	15 205 (28.7)	15 784 (29.8)	16 386 (30.9)	17 293 (32.6)	Hypertension, N (%)	53 919 (27.6)	6216 (36.7)
Type 2 diabetes, N (%)	2157 (4.1)	3248 (6.1)	4495 (8.5)	7017 (13.2)	Type 2 diabetes, N (%)		
Coronary heart disease, N (%)	6136 (11.6)	6512 (12.3)	6663 (12.6)	7033 (13.3)	Coronary heart disease, N (%)	21 132 (10.8)	5212 (30.8)

*SNP: single nucleotide polymorphism; †SD: standard deviation

Table 3. Mendelian randomization analysis of type 2 diabetes and risk of coronary heart disease, by sex, in UK Biobank*. Results indicate the increased risk of coronary heart disease per 1-log unit increase in genetic risk of type 2 diabetes (odds ratio [OR] and 95% confidence interval [CI]).

	Women		Men	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Two-stage residual inclusion estimation†	1.13 (1.08-1.18)	5.84×10^{-08}	1.21 (1.17-1.26)	2.31×10^{-24}
Weighted-median‡	1.04 (1.00-1.08)	0.067	1.06 (1.03-1.09)	<0.001
MR-Egger‡	1.01 (0.96-1.06)	0.81	1.00 (0.96-1.04)	0.99
MR PRESSO (outlier-corrected)‡	1.08 (1.05-1.13)	3.11×10^{-05}	1.13 (1.10-1.17)	1.57×10^{-12}
Sex-specific outliers removed†‡§	1.09 (1.05-1.14)	6.76×10^{-05}	1.24 (1.20-1.29)	2.78×10^{-27}
	Intercept (95% CI)	p-value	Intercept (95% CI)	p-value
MR-Egger (intercept)‡	0.002 (0.000-0.008)	0.027	0.008 (0.004, 0.011)	<0.001
Q-test‡	395.8		666.0	
I-squared‡	84.7%		87.1%	

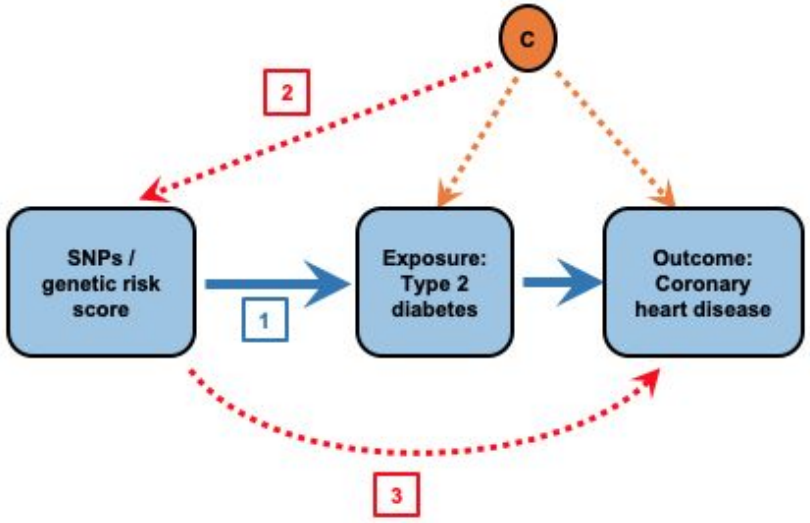
*Genetic instrument comprised of N=270 SNPs for type 2 diabetes identified in European DIAMANTE GWAS.

†Results from two-stage residual inclusion estimation using individual participant data and weighted genetic risk score in UK Biobank. Adjusted for age, genotype array, principle components of ancestry. P-value for interaction=0.02.

‡Results from summary-level analyses using SNP-type 2 diabetes estimates from DIAMANTE GWAS (excluding UK Biobank) and SNP-CHD estimates from UK Biobank. P-values for interaction: weighted median 0.43; MR-Egger 0.76; MR-PRESSO 0.07.

§Analysis with type 2 diabetes genetic instrument comprised of N=258 SNPs for women and N=245 SNPs for men, after SNPs identified as sex-specific outliers using radial MR excluded from genetic instrument. P-value for interaction <0.001.

Supplemental Figure 1.



Assumptions of Mendelian randomization: 1) The variants must be associated with the exposure of interest; 2) The variants must not be associated with confounders of the relationship between the exposure and the outcome; 3) The variants must be independent of the outcome except for their association via the exposure. SNP: single nucleotide polymorphism; C: Confounders

Supplemental Table 1. Details of the 270 single nucleotide polymorphisms (SNP) used as a genetic instrument for type 2 diabetes in Mendelian randomization analyses. Beta coefficients and standard errors (SE) for the association of each SNP with type 2 diabetes from the European DIAMANTE genome-wide association study. Outlier SNPs identified using radial MR.

					WOMEN		MEN		
SNP*	**Locus**	**Chr†**	**Effect Allele**	**Non-effect Allele**	**Beta**	**SE**	**Beta**	**SE**	**OUTLIER‡**
rs1005752	*HMG20A*	15	A	C	0.082	0.013	0.076	0.012	W,M
rs10096633	*LPL*	8	C	T	0.086	0.019	0.056	0.017	W
rs10097617	*TP53INP1*	8	T	C	0.05	0.012	0.043	0.011	
rs10193538	*BNIPL*	2	T	G	0.025	0.012	0.033	0.011	
rs10195252	*GRB14/COBLL1*	2	T	C	0.066	0.012	0.036	0.011	
rs10228066	*DGKB*	7	T	C	0.058	0.012	0.061	0.011	
rs10406327	*PEPD*	19	C	G	0.01	0.012	0.043	0.011	
rs10406431	*GIPR*	19	A	G	0.041	0.012	0.06	0.011	W
rs1042725	*HMGA2*	12	T	C	0.053	0.012	0.04	0.011	
rs1061810	*HSD17B12*	11	A	C	0.041	0.013	0.078	0.012	
rs10750397	*ETS1*	11	A	G	0.031	0.013	0.053	0.012	
rs10757283	*CDKN2A/B*	9	T	C	0.017	0.012	0.029	0.011	
rs10830963	*MTNR1B*	11	G	C	0.1	0.013	0.1	0.013	
rs10842994	*KLHDC5*	12	C	T	0.079	0.015	0.089	0.014	
rs10882101	*HHEX/IDE*	10	T	C	0.1	0.012	0.11	0.011	
rs10893829	*ETS1*	11	T	C	0.022	0.017	0.06	0.016	
rs10908278	*HNF1B*	17	T	A	0.052	0.012	0.083	0.011	
rs10937721	*WFS1*	4	C	G	0.071	0.012	0.096	0.011	
rs10938398	*GNPDA2*	4	A	G	0.056	0.012	0.042	0.011	
rs10954772	*PURG*	8	T	C	0.037	0.013	0.026	0.012	
rs10962	*HNF1B*	17	C	G	0.021	0.015	0.053	0.014	
rs10974438	*GLIS3*	9	C	A	0.035	0.013	0.055	0.012	

rs11042596	*INS/IGF2*	11	G	T	0.057	0.013	0.032	0.012	
rs11063028	*CCND2*	12	C	T	0.046	0.016	0.057	0.015	M
rs11070332	*LTK*	15	A	G	0.045	0.013	0.044	0.012	
rs11137820	*MTND2P8*	9	C	G	0.026	0.012	0.059	0.011	
rs11257655	*CDC123/CAMK1D*	10	T	C	0.08	0.014	0.09	0.013	
rs1127215	*PTGFRN*	1	C	T	0.048	0.012	0.046	0.011	
rs11496066	*FBXL13*	7	T	C	0.049	0.016	0.037	0.015	
rs115505614	*PAM*	5	T	C	0.15	0.029	0.17	0.026	M
rs11642430	*FAM57B*	16	G	C	0.034	0.012	0.048	0.011	
rs11680058	*FAM49A*	2	A	G	0.049	0.019	0.056	0.018	
rs11688682	*GLI2*	2	G	C	0.072	0.014	0.036	0.013	
rs11699802	*CEBPB*	20	C	T	0.037	0.012	0.041	0.011	
rs117001013	*YWHAH*	22	C	T	0.07	0.022	0.03	0.02	
rs11708067	*ADCY5*	3	A	G	0.1	0.015	0.08	0.014	
rs11709077	*PPARG*	3	G	A	0.11	0.019	0.11	0.017	
rs117483894	*TCF12*	15	G	A	0.12	0.031	0.077	0.029	
rs11759026	*CENPW*	6	G	A	0.062	0.014	0.059	0.013	W
rs11820019	*CCND1*	11	T	C	0.1	0.04	0.15	0.038	
rs11842871	*HMGB1*	13	G	T	0.051	0.014	0.028	0.013	
rs11926707	*KIF9*	3	C	T	0.048	0.013	0.029	0.012	
rs11967262	*VEGFA*	6	G	C	0.035	0.013	0.039	0.011	W
rs12001437	*UBAP2*	9	C	T	0.047	0.012	0.043	0.011	
rs12048743	*DSTYK*	1	G	C	0.043	0.012	0.039	0.011	
rs12140153	*PATJ*	1	G	T	0.065	0.021	0.039	0.02	
rs12454712	*BCL2A*	18	T	C	0.051	0.013	0.045	0.012	
rs1260326	*GCKR*	2	C	T	0.047	0.012	0.062	0.012	
rs12640250	*LCORL*	4	C	A	0.054	0.013	0.035	0.013	
rs12680028	*TRHR*	8	C	G	0.042	0.012	0.023	0.011	
rs12719778	*BOP1*	8	T	C	0.028	0.012	0.031	0.011	
rs12811407	*FBRSL1*	12	A	G	0.05	0.014	0.043	0.013	
rs12910825	*PRC1*	15	G	A	0.053	0.013	0.055	0.012	
rs12920022	*SPG7*	16	A	T	0.051	0.017	0.042	0.016	

rs1296328	*PABPC4L*	4	A	C	0.02	0.012	0.034	0.011	
rs13024606	*GRB14/COBLL1*	2	T	C	0.05	0.029	0.074	0.028	
rs13041756	*NKX2.2*	20	C	T	0.088	0.019	0.063	0.018	
rs13085136	*SHQ1*	3	C	T	0.05	0.025	0.058	0.023	
rs1316776	*DMGDH*	5	C	A	0.041	0.013	0.059	0.012	M
rs13426680	*CYTIP*	2	A	G	0.13	0.026	0.034	0.023	
rs1359790	*SPRY2*	13	G	A	0.057	0.013	0.085	0.013	
rs13737	*PTPN9*	15	G	T	0.04	0.014	0.044	0.014	
rs1377807	*ZZEF1*	17	C	G	0.059	0.013	0.054	0.012	W
rs140242150	*TCF7L2*	10	A	G	0.25	0.11	0.22	0.11	
rs1412234	*LINGO2*	9	C	T	0.061	0.013	0.032	0.012	
rs141521721	*PDE3B*	11	A	C	0.11	0.04	0.085	0.039	
rs1421085	*FTO*	16	C	T	0.13	0.012	0.11	0.011	
rs1426371	*WSCD2*	12	G	A	0.059	0.014	0.035	0.013	
rs145678014	*QSER1*	11	G	T	0.15	0.032	0.1	0.029	
rs145904381	*FAM63A*	1	T	C	0.11	0.061	0.3	0.056	
rs149364428	*CPQ*	8	A	G	0.27	0.061	0.18	0.058	
rs1493694	*NOTCH2*	1	T	C	0.084	0.019	0.087	0.018	M
rs1531583	*PCGF3*	4	T	G	0.11	0.028	0.095	0.026	
rs1561927	*PVT1*	8	C	T	0.038	0.013	0.046	0.013	
rs1562396	*KLF14*	7	G	A	0.081	0.013	0.029	0.012	
rs1580278	*SLC9B1*	4	C	A	0.052	0.012	0.029	0.011	
rs17013314	*UBE2E2*	3	G	A	0.13	0.033	0.12	0.031	
rs1708302	*JAZF1*	7	C	T	0.086	0.012	0.097	0.011	
rs17122772	*SLC7A7*	14	G	C	0.038	0.015	0.043	0.014	
rs17168486	*DGKB*	7	T	C	0.052	0.015	0.07	0.014	
rs17250977	*ANKH*	5	G	A	0.12	0.034	0.099	0.033	M
rs17261179	*ITGA1*	5	T	C	0.038	0.012	0.041	0.011	
rs17522122	*AKAP6*	14	T	G	0.031	0.012	0.045	0.011	
rs17684074	*WDR7*	18	G	C	0.033	0.014	0.046	0.013	M
rs17689007	*MSRA*	8	G	A	0.056	0.012	0.037	0.011	
rs177045	*NEUROG3*	10	G	A	0.064	0.013	0.054	0.012	

rs17772814	*CASC11*	8	G	A	0.081	0.024	0.12	0.022	
rs17791513	*TLE4*	9	A	G	0.094	0.025	0.12	0.022	
rs17802463	*DTNB*	2	G	T	0.037	0.014	0.043	0.013	
rs17819328	*PPARG*	3	G	T	0.035	0.012	0.029	0.011	
rs1783541	*MAP3K11*	11	T	C	0.076	0.015	0.036	0.014	
rs17836088	*NRXN3*	14	C	G	0.058	0.015	0.049	0.014	
rs1796330	*TSPAN8/LGR5*	12	G	C	0.049	0.012	0.062	0.011	
rs1800574	*HNF1A*	12	T	C	0.16	0.036	0.18	0.033	
rs1800961	*HNF4A*	20	T	C	0.17	0.032	0.11	0.029	
rs1801645	*PIM3*	22	C	T	0.041	0.014	0.045	0.013	
rs184509201	*TCF7L2*	10	C	G	0.18	0.052	0.15	0.048	
rs1903002	*FAM13A*	4	G	C	0.032	0.012	0.05	0.011	
rs2028150	*CEP68*	2	C	G	0.045	0.012	0.059	0.011	
rs2066827	*CDKN1B*	12	G	T	0.022	0.016	0.055	0.015	
rs2102278	*USP46*	4	G	A	0.038	0.013	0.011	0.012	
rs2197973	*USP44*	12	T	C	0.031	0.012	0.02	0.011	
rs2237895	*KCNQ1*	11	C	A	0.068	0.013	0.098	0.012	
rs2237897	*KCNQ1*	11	C	T	0.16	0.033	0.19	0.029	
rs2238689	*GIPR*	19	C	T	0.04	0.013	0.037	0.012	
rs2249105	*CEP68*	2	A	G	0.046	0.013	0.057	0.012	W
rs2258238	*HMGA2*	12	T	A	0.13	0.02	0.084	0.019	
rs2268078	*RALY*	20	A	G	0.029	0.013	0.051	0.012	M
rs2272163	*ROBO2*	3	C	A	0.044	0.012	0.033	0.012	
rs2280141	*PLEKHA1*	10	T	G	0.039	0.012	0.071	0.011	
rs2283220	*KCNQ1*	11	A	G	0.041	0.014	0.024	0.012	
rs2307111	*POC5*	5	T	C	0.07	0.012	0.039	0.011	
rs231349	*KCNQ1*	11	T	C	0.078	0.02	0.053	0.019	
rs231361	*KCNQ1*	11	A	G	0.052	0.014	0.06	0.013	M
rs243024	*BCL11A*	2	A	G	0.044	0.012	0.068	0.011	
rs2431115	*ANKRD55*	5	A	G	0.024	0.012	0.026	0.011	
rs2456530	*ONECUT1*	15	T	C	0.028	0.018	0.042	0.017	
rs2581787	*RFT1*	3	T	G	0.043	0.012	0.039	0.011	

rs2642588	*NEUROG3*	10	G	T	0.042	0.013	0.066	0.012	
rs2767036	*PDHX*	11	C	A	0.032	0.013	0.044	0.012	
rs2796441	*TLE1*	9	G	A	0.034	0.012	0.069	0.011	
rs279744	*ARL15*	5	C	A	0.049	0.013	0.03	0.012	
rs2800733	*SOGA3*	6	A	G	0.028	0.014	0.061	0.013	
rs2820446	*LYPLAL1*	1	C	G	0.068	0.013	0.057	0.012	M
rs28505901	*GPSM1*	9	G	A	0.076	0.016	0.086	0.015	
rs2872246	*ABCC5*	3	A	C	0.03	0.012	0.029	0.011	
rs28819812	*PDGFC*	4	C	A	0.032	0.015	0.05	0.014	
rs291367	*GNG4*	1	G	A	0.058	0.014	0.045	0.013	
rs2925979	*CMIP*	16	T	C	0.094	0.013	0.039	0.012	
rs2972144	*IRS1*	2	G	A	0.089	0.013	0.11	0.012	M
rs3111316	*FARSA*	19	A	G	0.053	0.012	0.025	0.011	
rs3217792	*CCND2*	12	C	T	0.08	0.024	0.1	0.022	
rs3217860	*CCND2*	12	G	A	0.042	0.014	0.051	0.013	
rs329122	*PHF15*	5	A	G	0.024	0.012	0.041	0.011	
rs340874	*PROX1*	1	C	T	0.049	0.012	0.07	0.011	
rs34298980	*LRFN2*	6	T	C	0.035	0.013	0.024	0.012	
rs34454109	*TSHZ2*	20	A	T	0.054	0.014	0.047	0.013	W
rs34584161	*RNF6*	13	A	G	0.025	0.014	0.068	0.013	M
rs34715063	*RASGRP1*	15	C	T	0.043	0.02	0.066	0.018	M
rs348330	*ABCB10*	1	G	A	0.032	0.013	0.058	0.012	
rs34855406	*MLX*	17	C	G	0.047	0.013	0.035	0.013	
rs34855922	*TCF7L2*	10	A	G	0.017	0.014	0.044	0.013	
rs34965774	*KSR2*	12	A	G	0.039	0.017	0.069	0.016	
rs35352848	*UBE2E2*	3	T	C	0.056	0.015	0.052	0.014	
rs35895680	*TTLL6*	17	C	A	0.05	0.013	0.05	0.012	M
rs35913461	*TMEM18*	2	C	T	0.06	0.016	0.042	0.015	
rs35999103	*PABPC1P2*	2	T	C	0.047	0.016	0.019	0.015	
rs362307	*HTT*	4	T	C	0.092	0.023	0.044	0.021	
rs3751837	*CLUAP1*	16	T	C	0.058	0.015	0.029	0.013	
rs3768321	*MACF1*	1	T	G	0.086	0.015	0.084	0.014	

rs3772071	*RBMS1*	2	T	C	0.055	0.013	0.044	0.013	
rs3774723	*PSMD6*	3	G	A	0.046	0.017	0.052	0.015	
rs3798519	*TFAP2B*	6	C	A	0.057	0.015	0.036	0.014	
rs3802177	*SLC30A8*	8	G	A	0.1	0.013	0.11	0.012	
rs3810291	*ZC3H4*	19	A	G	0.042	0.013	0.05	0.012	M
rs3811978	*ITGA1*	5	G	A	0.028	0.016	0.054	0.015	M
rs3845281	*ANKH*	5	G	A	0.068	0.021	0.058	0.019	
rs3887925	*ST6GAL1*	3	T	C	0.052	0.012	0.051	0.011	
rs39328	*RELN*	7	T	C	0.033	0.012	0.024	0.011	M
rs4148856	*MPHOSPH9*	12	C	G	0.053	0.015	0.049	0.014	
rs4238013	*CCND2*	12	C	T	0.062	0.015	0.059	0.014	
rs4279506	*IGF2BP3*	7	G	C	0.028	0.012	0.04	0.011	
rs4281707	*FTO*	16	G	A	0.028	0.012	0.029	0.011	
rs429358	*TOMM40/APOE*	19	T	C	0.079	0.018	0.1	0.016	W, M
rs4457053	*ZBED3*	5	G	A	0.065	0.013	0.067	0.012	
rs465002	*ANKRD55*	5	T	C	0.068	0.014	0.069	0.013	
rs4686471	*LPP*	3	C	T	0.058	0.012	0.047	0.011	
rs4688760	*RBM6*	3	T	C	0.027	0.013	0.039	0.012	
rs4709746	*QKI*	6	C	T	0.059	0.018	0.051	0.017	
rs474513	*SLC22A3*	6	A	G	0.043	0.012	0.032	0.011	W
rs4776970	*MAP2K5*	15	A	T	0.05	0.013	0.058	0.012	
rs4804833	*MAP2K7*	19	A	G	0.045	0.013	0.04	0.012	
rs4810426	*HNF4A*	20	T	C	0.092	0.019	0.072	0.018	
rs4925109	*RAI1*	17	A	G	0.066	0.013	0.038	0.012	
rs4929965	*INS/IGF2*	11	A	G	0.066	0.013	0.056	0.012	
rs4932265	*AP3S2*	15	T	C	0.052	0.013	0.078	0.013	
rs4946812	*BEND3*	6	G	A	0.038	0.013	0.036	0.012	
rs4977213	*BOP1*	8	C	T	0.05	0.013	0.056	0.012	
rs505922	*ABO*	9	C	T	0.066	0.013	0.044	0.012	
rs5213	*KCNJ11*	11	C	T	0.083	0.012	0.058	0.011	
rs523288	*MC4R*	18	T	A	0.037	0.014	0.041	0.013	
rs528350911	*WDR72*	15	G	C	0.31	0.078	0.27	0.075	

rs539515	*SEC16B*	1	C	A	0.082	0.015	0.028	0.014	
rs555759341	*INS/IGF2*	11	C	G	0.32	0.1	0.32	0.099	
rs55653563	*ZNF169*	9	A	C	0.042	0.013	0.048	0.013	
rs56337234	*MAEA*	4	C	T	0.067	0.013	0.039	0.012	
rs56348580	*HNF1A*	12	G	C	0.069	0.013	0.085	0.012	M
rs57235767	*MTNR1B*	11	C	T	0.038	0.013	0.046	0.012	
rs57327348	*XKR6*	8	A	T	0.068	0.015	0.043	0.014	
rs5758223	*EP300*	22	A	G	0.04	0.013	0.028	0.012	
rs576674	*KL*	13	G	A	0.061	0.016	0.061	0.015	
rs58432198	*FAF1*	1	C	T	0.041	0.019	0.061	0.018	
rs58730668	*ACSL1*	4	T	C	0.074	0.017	0.072	0.016	
rs601945	*MHC*	6	G	A	0.077	0.016	0.074	0.015	
rs60276348	*ACE*	17	T	C	0.042	0.018	0.061	0.017	
rs6063048	*EYA2*	20	G	A	0.044	0.013	0.039	0.013	
rs6070625	*GNAS*	20	G	C	0.03	0.012	0.041	0.011	
rs61676547	*BPTF*	17	C	G	0.05	0.015	0.082	0.014	
rs62007683	*MARK3*	14	G	T	0.035	0.013	0.031	0.012	
rs62080313	*COMMD9*	18	C	T	0.06	0.018	0.053	0.018	
rs62107261	*TMEM18*	2	T	C	0.13	0.032	0.071	0.029	
rs62271373	*TSC22D2*	3	A	T	0.12	0.028	0.052	0.026	
rs62492368	*AOC1*	7	A	G	0.044	0.013	0.037	0.012	
rs6458354	*VEGFA*	6	C	T	0.039	0.013	0.07	0.012	
rs6459733	*MNX1*	7	G	C	0.057	0.013	0.057	0.012	M
rs649961	*SLC12A8*	3	T	C	0.022	0.012	0.054	0.011	
rs6518681	*MTMR3/ASCC2*	22	G	A	0.096	0.023	0.09	0.021	
rs6545714	*BNIPL*	2	G	A	0.04	0.012	0.022	0.011	
rs6600191	*ITFG3*	16	T	C	0.062	0.016	0.06	0.015	
rs6708643	*THADA*	2	A	G	0.032	0.012	0.037	0.011	
rs67232546	*ETS1*	11	T	C	0.059	0.015	0.049	0.014	
rs6821438	*SMARCAD1*	4	A	G	0.048	0.012	0.044	0.011	M
rs6884702	*MRPS30*	5	G	A	0.05	0.012	0.045	0.011	
rs6885132	*ANKH*	5	C	G	0.051	0.021	0.055	0.02	

rs6976111	*CTTNBP2*	7	A	C	0.033	0.015	0.03	0.014	
rs7022807	*HAUS6*	9	G	A	0.056	0.012	0.023	0.011	
rs702634	*ARL15*	5	A	G	0.056	0.013	0.054	0.012	
rs703972	*ZMIZ1*	10	G	C	0.061	0.012	0.059	0.011	
rs7115753	*CRY2*	11	A	G	0.03	0.012	0.039	0.011	
rs7124681	*ELF1*	11	A	C	0.047	0.012	0.02	0.011	
rs71372253	*NF1*	17	C	T	0.045	0.025	0.11	0.024	
rs7178762	*USP3*	15	C	T	0.028	0.012	0.045	0.011	
rs718314	*ITPR2*	12	G	A	0.05	0.014	0.034	0.013	
rs7222481	*GLP2R*	17	C	G	0.044	0.013	0.03	0.012	
rs7240767	*LAMA1*	18	C	T	0.045	0.012	0.025	0.012	
rs7249758	*UHRF1*	19	A	G	0.044	0.015	0.04	0.014	
rs72802342	*BCAR1*	16	C	A	0.088	0.023	0.14	0.022	W
rs72926932	*TCF4*	18	C	A	0.085	0.021	0.087	0.02	
rs73226260	*HNF1A*	12	G	A	0.084	0.037	0.097	0.034	
rs738408	*PNPLA3*	22	T	C	0.037	0.014	0.066	0.013	
rs74452128	*MC4R*	18	C	A	0.17	0.042	0.14	0.038	
rs74653713	*MBNL1*	3	C	A	0.083	0.03	0.091	0.027	
rs75253922	*INSR*	19	C	T	0.041	0.015	0.029	0.015	
rs76263492	*CACNA2D3*	3	T	G	0.047	0.029	0.11	0.028	
rs7629630	*EGFEM1P*	3	A	T	0.041	0.017	0.065	0.016	
rs7645517	*ST6GAL1*	3	A	G	0.011	0.026	0.066	0.025	
rs76549217	*ANKH*	5	T	C	0.11	0.041	0.074	0.039	
rs7669833	*TMEM154*	4	T	A	0.044	0.013	0.07	0.012	
rs76895963	*CCND2*	12	T	G	0.42	0.056	0.51	0.052	
rs7719891	*RASA1*	5	G	A	0.034	0.014	0.046	0.013	
rs77464186	*CENTD2/ARAP1*	11	A	C	0.09	0.017	0.1	0.015	
rs7756992	*CDKAL1*	6	G	A	0.15	0.013	0.14	0.012	M
rs77864822	*RMST*	12	A	G	0.075	0.025	0.065	0.023	
rs78020297	*FTO*	16	A	G	0.041	0.028	0.038	0.025	
rs7867635	*FOCAD*	9	C	T	0.029	0.012	0.041	0.011	
rs7918400	*TCF7L2*	10	C	T	0.0092	0.012	0.021	0.011	

rs79687284	*PROX1*	1	C	G	0.15	0.035	0.17	0.033	
rs7987740	*IRS2*	13	T	C	0.042	0.012	0.013	0.011	
rs8010382	*SMEK1*	14	G	A	0.042	0.013	0.035	0.012	
rs80147536	*THADA*	2	A	T	0.08	0.021	0.16	0.02	
rs8017808	*CLEC14A*	14	G	T	0.043	0.014	0.015	0.013	
rs8032939	*RASGRP1*	15	C	T	0.058	0.014	0.026	0.013	
rs8037894	*C2CD4A/B*	15	G	C	0.046	0.012	0.051	0.011	
rs8046545	*ATP2A1*	16	G	A	0.033	0.013	0.028	0.012	
rs8107974	*TM6SF2*	19	T	A	0.061	0.022	0.11	0.021	M
rs862320	*NFAT5*	16	C	T	0.028	0.012	0.023	0.011	
rs878521	*GCK*	7	A	G	0.065	0.014	0.072	0.013	W
rs917195	*CRHR2*	7	C	T	0.055	0.015	0.052	0.014	
rs9379084	*RREB1*	6	G	A	0.099	0.02	0.051	0.019	
rs9430095	*SRGAP2*	1	C	G	0.015	0.012	0.043	0.011	
rs9494624	*SLC35D3*	6	A	G	0.041	0.013	0.059	0.012	
rs9505097	*RREB1*	6	C	T	0.032	0.015	0.054	0.014	
rs9537803	*PCDH17*	13	C	T	0.03	0.013	0.03	0.013	
rs9563615	*SRGAP2D*	13	A	T	0.032	0.013	0.023	0.012	
rs963740	*DLEU1*	13	A	T	0.024	0.013	0.056	0.013	
rs9687832	*ANKRD55*	5	A	G	0.076	0.015	0.041	0.014	
rs9828772	*TMCC1*	3	C	G	0.057	0.021	0.071	0.019	
rs9860730	*ADAMTS9*	3	A	G	0.067	0.013	0.066	0.012	M
rs9873618	*SLC2A2*	3	G	A	0.056	0.013	0.095	0.013	M
rs9957145	*GRP*	18	G	A	0.036	0.016	0.037	0.015	

*SNP: single nucleotide polymorphism
†Chr: Chromosome
‡Outliers identified using radial MR; W: women; M: men

Supplemental Table 2. Association of sex-specific genetic risk scores for type 2 diabetes with type 2 diabetes*. Genetic risk score comprised of 270 SNPs from the European DIAMANTE genome-wide association study.

	Women	**Men**
F statistic	683	1077
R-squared	0.02	0.03
Odds ratio (95% confidence interval)†	1.70 (1.66-1.73)	1.70 (1.67-1.73)

*Adjusted for age, genotype array, and four principal components of ancestry.
†Odds ratios for the risk of type 2 diabetes per standard deviation increase in type 2 diabetes genetic risk score.

Supplemental Table 3: Population Characteristics, UK Biobank (N=463 469), stratified by sex and coronary heart disease status.

	Women (N=251 420)				Men (N=212 049)			
	Without CHD (N=238 704)		With CHD (N=12 716)		Without CHD (N=185 705)		With CHD (N=26 344)	
Age, mean (SD*), years	56.3	(8.0)	61.6	(6.1)	56.3	(8.2)	61.5	(6.2)
Array type, No. (%)								
BiLEVE	23 257	(9.7)	1663	(13.1)	21 256	(11.4)	3641	(13.8)
Axiom	215 436	(90.3)	11 053	(86.9)	164 446	(88.9)	22 701	(86.2)
Type 2 diabetes, No. (%)	8071	(3.3)	1893	(14.9)	11 705	(6.3)	5212	(19.8)
Body mass index, mean (SD), kg/m^2	26.9	(5.1)	29.3	(5.8)	27.7	(4.2)	29.1	(4.6)
Waist circumference, mean (SD), cm	84.2	(12.3)	90.8	(13.8)	96.5	(11.1)	100.9	(12.0)
Smoking history, No. (%)								
Never	140 460	(58.8)	6061	(47.7)	93 156	(51.8)	8983	(34.1)
Previous	76 325	(32.0)	4927	(38.7)	69 566	(37.5)	13 404	(50.9)
Current	20 937	(8.8)	1637	(12.9)	22 237	(12.0)	3774	(14.3)
Dyslipidemia, No. (%)	21 515	(9.0)	4034	(31.7)	24 773	(13.3)	9070	(34.4)
Hypertension, No. (%)	51 335	(21.5)	6386	(50.2)	51 029	(27.5)	13 639	(51.8)
Systolic BP†, mean (SD), mmHg	135.1	(19.1)	140.1	(19.7)	141.0	(17.2)	141.4	(18.7)
Diastolic BP, mean (SD), mmHg	80.6	(9.9)	79.8	(10.5)	84.3	(9.8)	81.7	(10.6)

*SD: standard deviation; †BP: blood pressure